

FORM PTO-1390 (REV. 12-2001)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER <b>740-X02-007</b>	
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>				U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>10/049558</b>	
INTERNATIONAL APPLICATION NO. <b>PCT NO. DE00/06109</b>		INTERNATIONAL FILING DATE <b>JUNE 30, 2000</b>		PRIORITY DATE CLAIMED <b>AUGUST 14, 1999</b>	
TITLE OF INVENTION <b>ARTIFICIAL TEAR REPLACEMENT SOLUTION</b>					
APPLICANT(S) FOR DO/EO/US <b>DIRK-HENNING MENZ, JOACHIM DRESP AND MARTIN WINTER</b>					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.					
2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.					
3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.					
4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).					
5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))					
a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).					
b. <input checked="" type="checkbox"/> has been communicated by the International Bureau.					
c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).					
6. <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).					
a. <input checked="" type="checkbox"/> is attached hereto.					
b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).					
7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))					
a. <input checked="" type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).					
b. <input checked="" type="checkbox"/> have been communicated by the International Bureau.					
c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.					
d. <input type="checkbox"/> have not been made and will not be made.					
8. <input checked="" type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).					
9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).					
10. <input checked="" type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).					
<b>Items 11 to 20 below concern document(s) or information included:</b>					
11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.					
12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.					
13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.					
14. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.					
15. <input checked="" type="checkbox"/> A substitute specification.					
16. <input type="checkbox"/> A change of power of attorney and/or address letter.					
17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.					
18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).					
19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).					
20. <input checked="" type="checkbox"/> Other items or information:					
<b>CERTIFICATE OF EXPRESS MAILING; POSTCARD; MARKED-UP COPY OF SPECIFICATION; COPY OF EXAMINATION REPORT IN GERMAN AND ENGLISH</b>					

U.S. APPLICATION NO. <b>10/04/95 8</b> INTERNATIONAL APPLICATION NO. <b>PCT DE00/06109</b>				ATTORNEY'S DOCKET NUMBER <b>740-X02-007</b>			
21. <input checked="" type="checkbox"/> The following fees are submitted: <b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO . . . . . <b>\$1040.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO . . . . . <b>\$890.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO . . . . . <b>\$740.00</b>  International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) . . . . . <b>\$710.00</b>  International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) . . . . . <b>\$100.00</b>  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>CALCULATIONS PTO USE ONLY</b>          <table style="width:100%; border: none;"> <tr> <td style="width: 50%; border: none;"><b>\$ 890.00</b></td> <td style="width: 50%; border: none;"></td> </tr> </table>		<b>\$ 890.00</b>	
<b>\$ 890.00</b>							
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				<table style="width:100%; border: none;"> <tr> <td style="width: 50%; border: none;"><b>\$ 130.00</b></td> <td style="width: 50%; border: none;"></td> </tr> </table>		<b>\$ 130.00</b>	
<b>\$ 130.00</b>							
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE				
Total claims	<b>34 - 20 =</b>	<b>14</b>	<b>x \$18.00</b>	<b>\$ 252.00</b>			
Independent claims	<b>3 - 3 =</b>	<b>0</b>	<b>x \$84.00</b>	<b>\$</b>			
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			<b>+ \$280.00</b>	<b>\$</b>			
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$ 1272.00</b>			
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				+			
<b>SUBTOTAL =</b>				<b>\$ 1272.00</b>			
Processing fee of <b>\$130.00</b> for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				<b>\$</b>			
<b>TOTAL NATIONAL FEE =</b>				<b>\$ 1272.00</b>			
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00</b> per property +				<b>\$</b>			
<b>TOTAL FEES ENCLOSED =</b>				<b>\$ 1272.00</b>			
				Amount to be refunded: <b>\$</b>			
				charged: <b>\$</b>			

a. ☐ A check in the amount of \$ \_\_\_\_\_ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 500601 in the amount of \$ 1272.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 500601. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

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SIGNATURE  
**MARTIN FLEIT**  


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 NAME  
**16,900**  


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 REGISTRATION NUMBER

10/049558

Rec'd PCT/PTO 26 JUN 2002

PATENT

Attorney Docket No.: 740-X02-007

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant/Inventor: Dirk-Henning MENZ et al..

Application No.: 10/049,558

NATIONAL STAGE FILING OF PCT/EP00/06109

Group Art Unit:

Filed: February 14, 2002

Examiner:

For/Title: ARTIFICIAL TEAR REPLACEMENT SOLUTION

**SECOND PRELIMINARY AMENDMENT**

ASSISTANT COMMISSIONER FOR PATENTS  
WASHINGTON, D.C. 20231

Sir:

Please amend the above-identified application as follows.

**IN THE CLAIMS:**

Please amend claim 35 to read as follows:

35. (Amended) Method according to claim 34 comprising the further step of gelling the composition.

**REMARKS**

Claim 35 has been amended to depend from claim 34. A marked-up version of this claim showing additions and deletions is attached hereto.

Respectfully submitted,



Martin Fleit, Reg. #16,900

By PAUL D. BIANCO #43,500

Martin Fleit

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Applicant/Inventor: Dirk-Henning MENZ et al.  
Serial/Patent No.: NATIONAL STAGE FILING OF PCT/EP00/06109  
Filed/Issued: February 14, 2002  
For/Title: ARTIFICIAL TEAR REPLACEMENT SOLUTION

**Marked-Up Version of the Amended Claim**

Claim 35 was amended as follows, with additions underlined and deletions in brackets:

35. (Amended) Method [for the manufacture of a tear substitute composition]  
according to claim 34 comprising the further step of gelling the composition.

PATENT Attorney Docket No.: 740-X02-007  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant/Inventor: Dirk-Henning MENZ et al..

Serial/Patent No.: NATIONAL STAGE FILING OF PCT/DE00/06109

Group Art Unit:

Filed/Issued: February 14, 2002

Examiner:

For/Title: TEAR SUBSTITUTE

**PRELIMINARY AMENDMENT**

ASSISTANT COMMISSIONER FOR PATENTS  
WASHINGTON, D.C. 20231

Sir:

Kindly amend the above entitled application as follows.

Replace the abstract originally filed with the attached substitute ABSTRACT, a marked-up copy of the substitute ABSTRACT is attached.

IN THE SPECIFICATION:

Please substitute for the specification originally filed, the attached substitute specification, a marked-up copy of the substitute specification is attached.

IN THE CLAIMS:

Please cancel claims 1 to 17, and add new claims 18 to 51 as follows:

- - 18. Method for the external treatment of an eye of a mammal comprising applying to the eye a composition, which contains at least one water-soluble fluorinated surfactant, water and a nonpolar component, selected from the group consisting of a fluorocarbon, silicone and mixtures thereof.

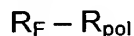
19. Method according to claim 18 wherein the composition is in the form of a gel.

20. Method according to claim 18 wherein the fluorocarbon is chosen from the group consisting of perfluoro compounds, partially fluorinated compounds having the general formula  $R_F R_H$  or  $R_F R_H R_F$ , fluoro oligomers of the type  $(R_F)_x R_H$ , and mixtures thereof.

21. Method according to claim 19 wherein the gel presents a polyaphron structure.

Applicant/Inventor: Dirk-Henning MENZ et al.  
 Serial/Patent No.: NATIONAL STAGE FILING OF PCT/DE00/06109  
 Filed/Issued: February 14, 2002  
 For/Title: TEAR SUBSTITUTE

22. Method according to claim 18 wherein the fluorinated surfactant is prepared according to the formula:



where  $R_F$  represents a linear or branched perfluoroalkyl group having more than 5 carbon atoms and  $R_{pol}$  represents a polar hydrocarbon residue which comprises at least one functional group, chosen from the series:

CO-NH(R), CO-NH(R)<sub>2</sub>, COO<sup>-</sup>, COOR, SO<sub>3</sub><sup>-</sup>, SO<sub>2</sub>-N(R)<sub>2</sub>, CH<sub>2</sub>-O-, R, PO<sub>2</sub>H, PO<sub>3</sub>H<sub>2</sub>,

where R represents an alkyl.

23. Method according to claim 18 wherein the molecular weight of the fluorinated surfactant is greater than 400 g/mol, and the surface tension of the fluorinated surfactant in an aqueous solution is smaller than 30 mNm.

24. Method according to claim 18 wherein the concentration of the fluorinated surfactant is less than the critical micellar formation concentration, and the concentration of the fluorocarbon is greater than 60 wt%.

25. Method according to claim 24 wherein the concentration of the fluorinated surfactant is less than 0.1%.

26. Method according to claim 24 wherein the concentration of the fluorocarbon is greater than 90 wt%.

27. Method according to claim 18 wherein the water-soluble fluorinated surfactant has at least six completely fluorinated hydrocarbons.

28. Method according to claim 19 wherein the gel has a refractive index of 1.334-1.338.

29. Method according to claim 19 including the further step of forming a thin film of the gel on the cornea.

30. Method according to claim 19 wherein the sum of the surface tension of the gel and the interfacial tension between the gel and the eye surface to which it is applied is smaller than the surface tension of the eye surface.

31. Method according to claim 19 including the further step of the gel becoming partly irreversibly liquefied under the effect of shearing stresses produced in the eye to which it is applied.

32. Method according to claim 19 wherein the application to the eye is effected by introducing the gel into the conjunctival sac, whereupon a gel-form reservoir is formed, part of the gel in the gel-form reservoir liquefying during each movement of the eyelid of the eye.

Applicant/Inventor: Dirk-Henning MENZ et al.  
 Serial/Patent No.: NATIONAL STAGE FILING OF PCT/DE00/06109  
 Filed/Issued: February 14, 2002  
 For/Title: TEAR SUSTITUTE

33. Method according to claim 32 wherein the liquefied portion of the gel forms a thin film on the cornea.

34. Method for the manufacture of a tear substitute composition comprising mixing together at least one water-soluble fluorinated surfactant, water and a nonpolar component selected from the group consisting of a fluorocarbon, a silicon and mixtures thereof.

35. Method for the manufacture of a tear substitute composition comprising the further step of gelling the composition.

36. Method according to claim 34 including the further step of sterilizing the composition after its components have been mixed together.

37. Method according to claim 35 including the further step of sterilizing the composition after gelling.

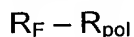
38. A composition for the external treatment of an eye of a mammal comprising a gel containing at least one water-soluble fluorinated surfactant, water and a nonpolar component selected from the group consisting of a fluorocarbon, silicone and mixtures thereof.

39. A composition for the external treatment of an eye of a mammal according to claim 38 wherein the composition is in the form of a gel.

40. A composition for the external treatment of an eye of a mammal according to claim 38 wherein the fluorocarbon is chosen from the group consisting of perfluoro compounds, partially fluorinated compounds having the general formula  $R_F R_H$  or  $R_F R_H R_F$ , fluoro oligomers of the type  $(R_F)_x R_H$ , and mixtures thereof.

41. A composition for the external treatment of an eye of a mammal according to claim 39 wherein the gel presents a polyaphron structure.

42. A composition for the external treatment of an eye of a mammal according to claim 38 wherein the fluorinated surfactant is characterized according to the formula:



where  $R_F$  represents a linear or branched perfluoroalkyl group having more than 5 carbon atoms and  $R_{pol}$  represents a polar hydrocarbon residue which comprises at least one functional group, chosen from the series:

CO-NH(R), CO-NH(R)<sub>2</sub>, COO-, COOR, SO<sub>3</sub>-, SO<sub>2</sub>-N(R)<sub>2</sub>, CH<sub>2</sub>-O-, R, PO<sub>2</sub>H, PO<sub>3</sub>H<sub>2</sub>,

where R represents an alkyl.

51. A composition for the external treatment of an eye of a mammal according to claim 50 wherein the liquefied part of the composition forms a thin film on the cornea. - -



Applicant/Inventor: Dirk-Henning MENZ et al..  
Serial/Patent No.: NATIONAL STAGE FILING OF PCT/DE00/06109  
Filed/Issued: February 14, 2002  
For/Title: TEAR SUBSTITUTE

### REMARKS

The application has been placed in better form for examination by the above changes.

Respectfully submitted,



Martin Fleit, Reg. #16,900

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SUBSTITUTE ABSTRACT

**ABSTRACT**

A tear replacement solution that contains at least one water-soluble fluorosurfactant, water and a non-polar component, preferably in gel form, and a method for the external treatment for the eye of an mammal by applying the tear replacement solution to the eye, preferably by placing in the conjunctival sac.

## SUBSTITUTE ABSTRACT – MARKED-UP

### Abstract

[ The invention relates to an artificial tear replacement solution for external eye treatment. Existing artificial tear replacement solutions have the disadvantage of exhibiting a short residence time in the cornea. The invention aims at providing an artificial tear replacement solution that is compatible over a long period, enables even moistening of the cornea and has a long residence time on the surface of the eye. This is achieved in that said] A tear replacement solution that contains at least one water-soluble fluorosurfactant, water and a non-polar component, preferably in gel form, and a method for the external treatment for the eye of an mammal by applying the tear replacement solution to the eye, preferably by placing in the conjunctival sac.

## SUBSTITUTE SPECIFICATION

### TEAR SUBSTITUTE

#### BACKGROUND OF THE INVENTION

##### Field of the Invention

**[0001]** The invention relates to a tear substitute for the external treatment of the eye.

##### Prior Art

**[0002]** Tear substitutes are used in the treatment of diseases of the eye, such as common keratoconjunctivitis sicca (so-called "dry eye"). Dry eye can be the result of different causes. The most frequent causes include reduction in tear production in the elderly, rheumatic or internal diseases (such as polyarthritis, diabetes and thyroid disease), diseases in which antibodies are raised against the body's own physiological substances (Sjögren's disease, Lupus erythematoses, sclerodermia), skin diseases, hormonal changes, neuroparalysis (such as after a stroke, defective position of the eyelid, decortication of tear glands), ingestion of certain drugs (such as  $\beta$  blockers, birth control pill, soporifics and tranquilizers), nutritional deficiency, climatic influences (heat, dry environmental air, season, air conditioners), environmental pollution (ozone, dust, solvent vapors, etc.), working in front of monitors, and chronic use of vessel contracting eyedrops (so-called whiteners). Furthermore, such eye diseases are also caused, but less frequently, by autoimmune diseases, diseases of the hematopoietic system, local eye diseases such as inflammation and trauma of the tear glands or hereditary diseases. The resulting dysfunctions impair or prevent the formation of a normal tear film, which has an exceedingly complicated structure in its natural form. There are essentially three components which participate in the formation of the tear film:

**[0003]** An internal mucin layer which covers the epithelial surface, followed by a middle aqueous layer, and a thin, external lipid layer. The mucin layer here functions as an adhesive component for the wetting of the cornea. The aqueous component moisturizes the cornea and it has a cleaning and protective function. The lipid component prevents evaporation of the aqueous component and prevents a quick runoff of the tear film.

**[0004]** Only an intact tear film can guarantee the full functionality of the eye surface over time, and, in addition to the mentioned defects, properties which reduce abrasion, antibacterial properties, and the oxygen supply of the cornea can be of

importance. The above-mentioned components of tears are continuously produced. The formation of a thin tear film over the cornea occurs spontaneously with each blink of the eyelid, as, during the downward movement of the upper lid, the external lipid layer of the tear film is compressed between the lid margins, where the aqueous layer essentially remains in its position. As soon as a part of the production of the tear components is interrupted or disturbed, or there is a mechanical obstacle to the formation of the tear film as a result of the blinking of the eyelid, corresponding complaints arise from, for instance the so-called sand grain effect to massive visual disorders, which in extreme cases, can lead to blindness as a result of irreversible damage to the cornea.

**[0005]** As there are a multitude of possible causes of "dry eye" and as the problem of the tear film [formation] is complex, a multitude of treatment agents are known from the state of the art. In this context, examples are the patents EP 698 388, DE 195 11 322, DE 43 03 818, EP 801 948, WO 97/45102, and WO 96/33695.

**[0006]** In the above-mentioned patents, descriptions are essentially provided of treatment agents which, as a result of introduction into the conjunctival sac, replace one or more missing components of natural tear film. The replacement is here carried out using substances which, having an appropriate retention time, take over the protective and abrasion-reducing functions, and possess the same or at least similar properties as the components to be substituted. The treatment agent which is commercially available under the trade name "Liposic," for example, constitutes an attempt to duplicate all the natural tear components in a so-called three-dimensional tear.

**[0007]** The liquid treatment agents which are known from the state of the art, however, all present the drawback of having a relatively short residence time on the cornea. As a result, the treatment agent must be introduced at regular intervals into the eye, which can be very inconvenient and unpleasant for the patient. In the known gel form treatment agents, this drawback is at least partially avoided. However, in the case of gel form treatment agents, it was shown to be difficult to supply sufficient oxygen to the cornea.

**[0008]** In the patents EP 089 815 and EP 112 658, ophthalmological treatment agents for lubrication and protection of the eye surface are proposed which contain a perfluorocarbon or a substituted derivative thereof. The substantial advantages compared to conventional treatment agents that are mentioned are here the immiscibility with water and the high gas dissolution capacity, particularly for oxygen.

**[0009]** Because of the known high oxygen dissolution capacity of fluorocarbons, the treatment agent described in the above patents is said to guarantee a sufficient oxygen supply for the cornea. In addition, because of the high density of the

perfluorocarbons, a long residence time on the cornea is said to be possible because the compounds are said to become enriched due to their high specific weight.

Moreover, it is claimed that, because of the insolubility of the treatment agent in water, the use of preservatives could be omitted.

**[0010]** However, the drawbacks of these perfluorocarbon-containing treatment agents are that an intact mucin layer and sufficient secretion of lipids must be guaranteed to allow sufficient functionality of the agent on the cornea. Additional drawbacks result from impaired vision as a result of the formation of streaks, as well as the risk of obstructing the tear drainage ducts, caused by the immiscibility of the perfluorocarbons with water. Moreover, the immiscibility of perfluorocarbon and water, as well as the large interfacial tension between aqueous and perfluorocarbon-containing areas lead to the formation of diffusion barriers, which prevents a sufficient supply [of oxygen] to the cornea.

**[0011]** In addition, different forms of fluorogels are known from the state of the art, which were also proposed for medicinal applications. From US 5,573,757 and EP 340 079 as well as WO 97/03644, polyaphron gels are known whose structure is stabilized by fluorinated surfactants. The structure and the properties of polyaphron gels are described, for example, in Chapter 8 of Foams and Biliquid Foams-Aphrons, F. Sebba, John Wiley, 1987.

**[0012]** Fluorogels as such, in general, present a pronounced viscoelasticity. These substances therefore are not suitable for an extraocular treatment of eye diseases, because the absence of a pronounced property of film formation does not allow an even distribution and wetting of the cornea.

**[0013]** Therefore, the problem of the present invention is to provide a tear substitute which is tolerated over the long term, which allows even wetting of the cornea, which presents a long retention time on the eye surface, and which guarantees the supply of oxygen and water-soluble nutrients to the cornea.

## **SUMMARY OF THE INVENTION**

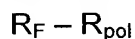
**[0014]** This problem is solved by using and/or applying to a person's or animal's eye a tear substitute for external treatment of the eye, characterized in that it contains at least one water-soluble fluorinated surfactant, water and a nonpolar component. In particular, the nonpolar component is a fluorocarbon or a silicone oil.

## **DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**

**[0015]** There will now be described in detail the present invention and how the novel compositions of the present invention are formulated, and how they are used by

applying to a person's or animal's eye. Essentially the tear substitute composition of the invention contains at least one water-soluble fluorinated surfactant, water and a nonpolar component. In particular, the nonpolar component is a fluorocarbon or a silicone oil. The fluorocarbon is chosen from the group comprising perfluoro compounds, partially fluorinated compounds having the general formula  $R_F R_H$  or  $R_F R_H R_F$ , as well as, fluoro oligomers of the type  $(R_F)_x R_H$ , or a mixture thereof.

**[0016]** The tear substitute according to one aspect of the invention is characterized in that it is in the form of a gel and presents a polyaphron structure. The fluorinated surfactant is prepared according to the general formula:



where  $R_F$  represents a linear or branched perfluoroalkyl group having more than 5 carbon atoms and  $R_{pol}$  represents a polar hydrocarbon residue which comprises at least one functional group chosen from the series:

$CO-NH(R)$ ,  $CO-NH(R)_2$ ,  $COO^-$ ,  $COOR$ ,  $SO_3^-$ ,  $SO_2-N(R)_2$ ,  $CH_2-O-$ ,  $R$ ,  $PO_2H$ ,  $PO_3H_2$ , where  $R$  represents an alkyl.

**[0017]** The tear substitute according to the invention is characterized in that the molecular weight of the fluorinated surfactant is greater than 400 g/mol, and the surface tension of the fluorinated surfactant in an aqueous solution is less than 30 mNm. Further, according to the invention, the tear substitute is characterized in that the concentration of the fluorinated surfactant is less than critical micellar formation concentration, preferably less than 0.1%, and the concentration of the fluorocarbon is greater than 60 wt%, preferably greater than 90 wt%.

**[0018]** In a more specific aspect of the invention, the tear substitute is characterized in that the water-soluble fluorinated surfactant presents at least 6 completely fluorinated carbon atoms.

**[0019]** The tear substitute according to the invention is characterized in that it presents a refractive index of from 1.334 to 1.338.

**[0020]** As taught by the invention, the tear substitute is characterized in that the tear substitute on the cornea forms a thin film. The sum of the surface tension of the tear substitute and the interfacial tension between the tear substitute and the surface of the eye is smaller than the surface tension of the surface of the eye. When applied to an eye, the gel of tear substitute liquefies at least partially irreversibly under the effect of shearing stresses. It is preferred that the tear substitute be introduced into the conjunctival sac where the tear substitute forms a gel-form reservoir, a part of which liquefies during each blink of the eyelid. The liquefied portion of the tear substitute on the cornea forms a thin film.

**[0021]** One of the essential foundations of the present invention consists of the knowledge that a preparation which contains water, a nonpolar component and a water-soluble fluorinated surfactant, evenly wets smooth hydrophobic surfaces as soon as the preparation is in liquid form. The mechanism which effects the even distribution of the liquid preparation as a thin film on the smooth surface is the spreading of the immiscible components of the preparation according to the invention on top of each other, or on the hydrophilic or hydrophobic surface.

**[0022]** As a result, with the tear substitutes according to the invention, it is possible to achieve film formation from a water-containing preparation on the hydrophobic cornea. The formation of the thin film on the cornea here occurs as a result of blinking of the eyelid, as in natural tear formation. In this context, it is particularly the combination of hydrophilic, hydrophobic and fluorophilic properties, resulting from the structure of the fluorinated surfactants, which is used for the wetting of the cornea surface. By maintaining certain concentrations of the fluorinated surfactants it is possible, in addition, to adjust the surface and interfacial tensions of the components of the invention in such a manner that an optimal film formation and sufficient supply of oxygen to the cornea are possible.

**[0023]** The formation of thin films on the cornea surface leads to high residence capacities for the preparations and at the same time to the absence of prevention of tear secretion, mucus production and secretion of the marginal eyelid glands. Additionally, the resulting films prevent adhesion of the lid. In addition, the special surface properties of the preparation allow their passage, at the end of the residence time, into the natural tear drainage ducts without obstructing them. In this manner, the preparations according to the invention can take over the abrasion reducing and wetting functions of natural tear film without causing undesired side effects such as obstructed tear drainage ducts.

**[0024]** As a result of the combination of the components of the tear substitute according to the invention, it is possible to benefit from the advantages of the individual components without having to take into account any drawbacks.

**[0025]** The wetting properties of surfactants are well known, and they are used in many industrial processes. However, it is precisely these intrinsically advantageous properties which are the cause of their poor biocompatibility, which is reflected above all in dysfunctions in cell membranes. Therefore, the use of surfactant-containing substances in medical applications is strongly limited because of toxic behavior. Thus, for example, incompatibilities of oxygen-transporting emulsions can be explained by the effect of the surfactants which they contain. In particular, it appears that the use of



**[0027]** In addition, the damaging effects of the fluorinated surfactants in the preparations according to the invention are further repressed by the effects of the nonpolar components. This is achieved by the fixing of the fluorinated surfactants in the nonpolar matrix, resulting in a lowering of the surface tension of the aqueous components, without destroying the conditions which are caused by the natural surfactant compounds of the tear film. In this context, one exploits the fact that the interactions of the fluorinated surfactants with the nonpolar components are stronger than with the lipophilic components of the eye surface.

**[0029]** As nonpolar components, fluorocarbons or silicone oil are particularly suited. If fluorocarbons are used as nonpolar components, the known advantageous properties of these substances, such as the high oxygen solubility and the lubricating and protecting function, can be exploited. As a result of the oxygen-transporting properties of the fluorocarbons, the cornea is sufficiently supplied with oxygen without impairing vision due to irregular layer thicknesses or milky emulsions, and without the formation of barrier layers between the hydrophobic cornea and the lipophobic fluorocarbons, which prevent oxygen transfer. In this context, it should be emphasized that fluorocarbon does not need a carrier (as, for example, in EP 089 815), rather it acts itself as a carrier for the fluorinated surfactants.

**[0030]** The formation of thin films as a result of the blinking of the eyelid and the spreading of the nonmiscible components not only leads to good gliding properties of the tear substitute according to the invention, in addition, because of the resulting fine distribution, it also is responsible for an increased residence duration on the surface. The latter effect is further supported by the fact that the thin film spontaneously seeks the lowest possible layer thicknesses, while the chosen surface and boundary properties at the same time act against rupturing of the films. By an appropriate selection of the components of the tear substitute, the surface tension of the tear substitute and the interfacial tension between the tear substitute and eye surface can be adjusted in such a manner that the sum of the two magnitudes is greater than the surface tension of the surface of the eye. This allows, in particular, improved film formation as a result of spreading on the eye surface. The film-like layer structures produced by spreading can take over the function of the natural tear film, where the cornea is wetted and protected without the need to hydrophilize the cornea surface.

**[0031]** The sliding properties and the residence duration can be further improved if the tear substitute according to the invention is first in the form of a polyaphron gel. It was found that such gels made of the components according to the invention decompose to the liquid condition as a result of the high shear stresses generated during blinking of the eyelid. This decomposition is irreversible as soon as the polyaphron structure is completely destroyed in the entire volume of the gel. It was shown that, as a result of shearing stresses, produced, for example, during the blinking of an eyelid, a certain volume of the gel is released as a result of irreversible liquefaction, and the liquefied portion of the gel is then evenly distributed on smooth surfaces due to spreading of the immiscible components, in the form of a thin film. Advantageously, the gel-form tear substitute is introduced into the conjunctival sac, where it forms a gel-form reservoir. During each blinking of the eyelid, a portion of the gel is liquefied and then it is finely and evenly distributed, in the form of a thin film, over the cornea surface.

**[0032]** With the described preparations according to the invention, the requirements for a tear substitute are successfully and excellently met. In this context, it should be mentioned, in particular, that although individual components intrinsically contribute important functions, it is only the combination of the individual components which allows the combination of the excellent properties of the fluorinated surfactants and the nonpolar components.

**[0033]** In this context, it is particularly the combination of the oxygen-transporting properties and the uptake capacity for water-soluble nutrients with the properties of high

transparence and good film formation, which is of crucial importance. In addition to the replacement of functions such as wetting, reduction of abrasion, supply of nutrients and oxygen, additional properties of the preparations can also be used, such as the lipophobic properties of the preparations, leading to a reduction in the deposition of sebum, and the absence of sticking of the eyelid. An additional advantage results from the preservative properties of the nonpolar components of which not all the manufacturing steps must be carried out under sterile conditions. This means the preparations can be sterilized after the manufacture, for example, by treatment at 121°C for 15 min in autoclaves, where the use of additional preservatives can be omitted.

**[0034]** The following examples should further explain the manufacture and the use of preparations according to the invention.

**[0035]** Example 1

0.1 g Fluowet® (trade name, the company Clariant) OTL, 0.9 g water and 99 g perfluorophenanthrene (having a surface tension of  $\sigma = 19$  mNm) are homogenized, sterilized at 121°C for 15 min, and then applied by means of syringe to a mirror and distributed, where the surface is wetted by an even, nonrupturing film.

**[0036]** Example 2

Polyaphron gels are prepared by known methods from tetraethylpiperazinium salt of perfluorooctanoic acid ( $\sigma = 15.9$  mNm; 0.1 g), balanced salt solution (BSS); 0.9 g and perfluorophenanthrene ( $\sigma = 19$  mNm; 99 g) or perfluoroalkylethanol oxethylate ( $\sigma = 19$  mNm; 0.1 g) BSS (0.9 g) and perfluorophenanthrene ( $\sigma = 19$  mNm; 99 g), and sterilized at 121°C for 15 min in the autoclave. The gel-form preparations were filled into syringes and investigated by a Draize test. No irritations occurred during the Draize test. Even two weeks after application of the gel, the tear secretion, mucus production or secretion of the lid margin glands in rabbits was not impaired. Even after continuation of daily treatment for 16 weeks, no signs of incompatibility were observed.

**[0037]** Example 3

A preparation prepared according to Example 1 is applied to the eyes of rabbits. A short time after application, a known treatment agent for enlarging the pupils is applied. It was observed that the pupil-enlarging agent loses its effect as soon as a thin film of the tear substitute according to the invention has formed on the cornea. This observation serves as a demonstration of the capacity of the preparation according to

the invention to form thin closed films over the cornea, as with the natural tear. In addition, this example shows that the preparations according to the invention have a protective function, by preventing water-containing or water-soluble substance from coming in contact with the eye surface as soon as a film has formed on the cornea.

**[0038]** Example 4

From a 10% solution of perfluorooctanoic acid tetraethylpiperazinium salt (having surface tension  $\sigma = 15.9$  mNm) in water and highly purified silicone oil 1000 mPas, a gel is produced by foaming the aqueous solution and introduction of the silicone oil. After sterilization at 121°C for 15 min, this preparation is applied to a water-loaded surface. Spontaneous spreading occurs.

**SUBSTITUTE SPECIFICATION (MARKED UP)****TEAR SUBSTITUTE****BACKGROUND OF THE INVENTION****Field of the Invention**

**[0001]** The invention relates to a tear substitute for the external treatment of the eye.

**Prior Art**

**[0002]** Tear substitutes are used in the treatment of diseases of the eye, such as common keratoconjunctivitis sicca (so-called "dry eye"). Dry eye can be the result of different causes. The most frequent causes include reduction in tear production in the elderly, rheumatic or internal diseases (such as polyarthritis, diabetes and thyroid disease), diseases in which antibodies are raised against the body's own physiological substances (Sjögren's disease, Lupus erythematosus, scleroderma), skin diseases, hormonal changes, neuroparalysis (such as after a stroke, defective position of the eyelid, decortication of tear glands), ingestion of certain drugs (such as  $\beta$  blockers, birth control pill, soporifics and tranquilizers), nutritional deficiency, climatic influences (heat, dry environmental air, season, air conditioners), environmental pollution (ozone, dust, solvent vapors, etc.), working in front of monitors, and chronic use of vessel contracting eyedrops (so-called whiteners). Furthermore, such eye diseases are also caused, but less frequently, by autoimmune diseases, diseases of the hematopoietic system, local eye diseases such as inflammation and trauma of the tear glands or hereditary diseases. The resulting dysfunctions impair or prevent the formation of a normal tear film, which has an exceedingly complicated structure in its natural form. There are essentially three components which participate in the formation of the tear film:

**[0003]** An internal mucin layer which covers the epithelial surface, followed by a middle aqueous layer, and a thin, external lipid layer. The mucin layer here functions as an adhesive component for the wetting of the cornea. The aqueous component moisturizes the cornea and it has a cleaning and protective function. The lipid component prevents evaporation of the aqueous component and prevents a quick runoff of the tear film.

**[0004]** Only an intact tear film can guarantee the full functionality of the eye surface over time, and, in addition to the mentioned defects, properties which reduce

abrasion, antibacterial properties, and the oxygen supply of the cornea can be of importance. The above-mentioned components of tears are continuously produced. The formation of a thin tear film over the cornea occurs spontaneously with each blink of the eyelid, as, during the downward movement of the upper lid, the external lipid layer of the tear film is compressed between the lid margins, where the aqueous layer essentially remains in its position. As soon as a part of the production of the tear components is interrupted or disturbed, or there is a mechanical obstacle to the formation of the tear film as a result of the blinking of the eyelid, corresponding complaints arise from, for instance the so-called sand grain effect to massive visual disorders, which in extreme cases, can lead to blindness as a result of irreversible damage to the cornea.

**[0005]** As there are a multitude of possible causes of "dry eye" and as the problem of the tear film [formation] is complex, a multitude of treatment agents are known from the state of the art. In this context, examples are the patents EP 698 388, DE 195 11 322, DE 43 03 818, EP 801 948, WO 97/45102, and WO 96/33695.

**[0006]** In the above-mentioned patents, descriptions are essentially provided of treatment agents which, as a result of introduction into the conjunctival sac, replace one or more missing components of natural tear film. The replacement is here carried out using substances which, having an appropriate retention time, take over the protective and abrasion-reducing functions, and possess the same or at least similar properties as the components to be substituted. The treatment agent which is commercially available under the trade name "Liposic," for example, constitutes an attempt to duplicate all the natural tear components in a so-called three-dimensional tear.

**[0007]** The liquid treatment agents which are known from the state of the art, however, all present the drawback of having a relatively short residence time on the cornea. As a result, the treatment agent must be introduced at regular intervals into the eye, which can be very inconvenient and unpleasant for the patient. In the known gel form treatment agents, this drawback is at least partially avoided. However, in the case of gel form treatment agents, it was shown to be difficult to supply sufficient oxygen to the cornea.

**[0008]** In the patents EP 089 815 and EP 112 658, ophthalmological treatment agents for lubrication and protection of the eye surface are proposed which contain a perfluorocarbon or a substituted derivative thereof. The substantial advantages compared to conventional treatment agents that are mentioned are here the immiscibility with water and the high gas dissolution capacity, particularly for oxygen.

**[0009]** Because of the known high oxygen dissolution capacity of fluorocarbons, the treatment agent described in the above patents is said to guarantee a sufficient

oxygen supply for the cornea. In addition, because of the high density of the perfluorocarbons, a long residence time on the cornea is said to be possible because the compounds are said to become enriched due to their high specific weight. Moreover, it is claimed that, because of the insolubility of the treatment agent in water, the use of preservatives could be omitted.

**[0010]** However, the drawbacks of these perfluorocarbon-containing treatment agents are that an intact mucin layer and sufficient secretion of lipids must be guaranteed to allow sufficient functionality of the agent on the cornea. Additional drawbacks result from impaired vision as a result of the formation of streaks, as well as the risk of obstructing the tear drainage ducts, caused by the immiscibility of the perfluorocarbons with water. Moreover, the immiscibility of perfluorocarbon and water, as well as the large interfacial tension between aqueous and perfluorocarbon-containing areas lead to the formation of diffusion barriers, which prevents a sufficient supply [of oxygen] to the cornea.

**[0011]** In addition, different forms of fluorogels are known from the state of the art, which were also proposed for medicinal applications. From US 5,573,757 and EP 340 079 as well as WO 97/03644, polyaphron gels are known whose structure is stabilized by fluorinated surfactants. The structure and the properties of polyaphron gels are described, for example, in Chapter 8 of Foams and Biliquid Foams-Aphrons, F. Sebba, John Wiley, 1987.

**[0012]** Fluorogels as such, in general, present a pronounced viscoelasticity. These substances therefore are not suitable for an extraocular treatment of eye diseases, because the absence of a pronounced property of film formation does not allow an even distribution and wetting of the cornea.

**[0013]** Therefore, the problem of the present invention is to provide a tear substitute which is tolerated over the long term, which allows even wetting of the cornea, which presents a long retention time on the eye surface, and which guarantees the supply of oxygen and water-soluble nutrients to the cornea.

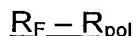
## **SUMMARY OF THE INVENTION**

**[0014]** This problem is solved by [the characterizing portions of Claim 1. Advantageous embodiment examples can be obtained from the secondary claims.] using and/or applying to a person's or animal's eye a tear substitute for external treatment of the eye, characterized in that it contains at least one water-soluble fluorinated surfactant, water and a nonpolar component. In particular, the nonpolar component is a fluorocarbon or a silicone oil.

## **DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS**

**[0015]** There will now be described in detail the present invention and how the novel compositions of the present invention are formulated, and how they are used by applying to a person's or animal's eye. Essentially the tear substitute composition of the invention contains at least one water-soluble fluorinated surfactant, water and a nonpolar component. In particular, the nonpolar component is a fluorocarbon or a silicone oil. The fluorocarbon is chosen from the group comprising perfluoro compounds, partially fluorinated compounds having the general formula  $R_F R_H$  or  $R_F R_H R_F$ , as well as, fluoro oligomers of the type  $(R_F)_x R_H$ , or a mixture thereof.

**[0016]** The tear substitute according to one aspect of the invention is characterized in that it is in the form of a gel and presents a polyaphron structure. The fluorinated surfactant is prepared according to the general formula:



where  $R_F$  represents a linear or branched perfluoroalkyl group having more than 5 carbon atoms and  $R_{pol}$  represents a polar hydrocarbon residue which comprises at least one functional group chosen from the series:

CO-NH(R), CO-NH(R)<sub>2</sub>, COO-, COOR, SO<sub>3</sub>-, SO<sub>2</sub>-N(R)<sub>2</sub>, CH<sub>2</sub>-O-, R, PO<sub>2</sub>H, PO<sub>3</sub>H<sub>2</sub>, where R represents an alkyl.

**[0017]** The tear substitute according to the invention is characterized in that the molecular weight of the fluorinated surfactant is greater than 400 g/mol, and the surface tension of the fluorinated surfactant in an aqueous solution is less than 30 mNm. Further, according to the invention, the tear substitute is characterized in that the concentration of the fluorinated surfactant is less than critical micellar formation concentration, preferably less than 0.1%, and the concentration of the fluorocarbon is greater than 60 wt%, preferably greater than 90 wt%.

**[0018]** In a more specific aspect of the invention, the tear substitute is characterized in that the water-soluble fluorinated surfactant presents at least 6 completely fluorinated carbon atoms.

**[0019]** The tear substitute according to the invention is characterized in that it presents a refractive index of from 1.334 to 1.338.

**[0020]** As taught by the invention, the tear substitute is characterized in that the tear substitute on the cornea forms a thin film. The sum of the surface tension of the tear substitute and the interfacial tension between the tear substitute and the surface of the eye is smaller than the surface tension of the surface of the eye. When applied to an eye, the gel of tear substitute liquefies at least partially irreversibly under the effect of shearing stresses. It is preferred that the tear substitute be introduced into the



conjunctival sac where the tear substitute forms a gel-form reservoir, a part of which liquefies during each blink of the eyelid. The liquefied portion of the tear substitute on the cornea forms a thin film.

**[0021]** One of the essential foundations of the present invention consists of the knowledge that a preparation which contains water, a nonpolar component and a water-soluble fluorinated surfactant, evenly wets smooth hydrophobic surfaces as soon as the preparation is in liquid form. The mechanism which effects the even distribution of the liquid preparation as a thin film on the smooth surface is the spreading of the immiscible components of the preparation according to the invention on top of each other, or on the hydrophilic or hydrophobic surface.

**[0022]** As a result, with the tear substitutes according to the invention, it is possible to achieve film formation from a water-containing preparation on the hydrophobic cornea. The formation of the thin film on the cornea here occurs as a result of blinking of the eyelid, as in natural tear formation. In this context, it is particularly the combination of hydrophilic, hydrophobic and fluorophilic properties, resulting from the structure of the fluorinated surfactants, which is used for the wetting of the cornea surface. By maintaining certain concentrations of the fluorinated surfactants it is possible, in addition, to adjust the surface and interfacial tensions of the components of the invention in such a manner that an optimal film formation and sufficient supply of oxygen to the cornea are possible.

**[0023]** The formation of thin films on the cornea surface leads to high residence capacities for the preparations and at the same time to the absence of prevention of tear secretion, mucus production and secretion of the marginal eyelid glands. Additionally, the resulting films prevent adhesion of the lid. In addition, the special surface properties of the preparation allow their passage, at the end of the residence time, into the natural tear drainage ducts without obstructing them. In this manner, the preparations according to the invention can take over the abrasion reducing and wetting functions of natural tear film without causing undesired side effects such as obstructed tear drainage ducts.

**[0024]** As a result of the combination of the components of the tear substitute according to the invention, it is possible to benefit from the advantages of the individual components without having to take into account any drawbacks.

**[0025]** The wetting properties of surfactants are well known, and they are used in many industrial processes. However, it is precisely these intrinsically advantageous properties which are the cause of their poor biocompatibility, which is reflected above all in dysfunctions in cell membranes. Therefore, the use of surfactant-containing

substances in medical applications is strongly limited because of toxic behavior. Thus, for example, incompatibilities of oxygen-transporting emulsions can be explained by the effect of the surfactants which they contain. In particular, it appears that the use of surfactant-containing substances as tear substitutes is ruled out, because the function of the natural tear film is decisively effected by the surface-modifying properties of the lipids, and the latter react particularly sensitively to additives of other surfactant substances.

**[0026]** However, by the combination of the components of the tear substitute according to the invention, the surface active effect of the surfactants was, nevertheless, unexpectedly exploited, without impairment of the function of the surfactant compounds present in the natural tear film. The fluorinated surfactants used according to the invention, in this context, are characterized, in contrast to other known surfactants, by an improved biocompatibility. Fluorinated surfactants by themselves offer an improved biocompatibility, compared to nonfluorine-containing emulsifiers, combined with an unusual surface activity.

**[0027]** In addition, the damaging effects of the fluorinated surfactants in the preparations according to the invention are further repressed by the effects of the nonpolar components. This is achieved by the fixing of the fluorinated surfactants in the nonpolar matrix, resulting in a lowering of the surface tension of the aqueous components, without destroying the conditions which are caused by the natural surfactant compounds of the tear film. In this context, one exploits the fact that the interactions of the fluorinated surfactants with the nonpolar components are stronger than with the lipophilic components of the eye surface.

**[0028]** In this manner, the known surfactant properties of surfactants can be exploited for extraocular applications. In combination with the properties of water and the nonpolar matrix, the fluorinated surfactants provide the film-forming properties of the preparations according to the invention, and thus they allow an even thin-film wetting of the cornea.

**[0029]** As nonpolar components, fluorocarbons or silicone oil are particularly suited. If fluorocarbons are used as nonpolar components, the known advantageous properties of these substances, such as the high oxygen solubility and the lubricating and protecting function, can be exploited. As a result of the oxygen-transporting properties of the fluorocarbons, the cornea is sufficiently supplied with oxygen without impairing vision due to irregular layer thicknesses or milky emulsions, and without the formation of barrier layers between the hydrophobic cornea and the lipophobic fluorocarbons, which prevent oxygen transfer. In this context, it should be emphasized

that fluorocarbon does not need a carrier (as, for example, in EP 089 815), rather it acts itself as a carrier for the fluorinated surfactants.

**[0030]** The formation of thin films as a result of the blinking of the eyelid and the spreading of the nonmiscible components not only leads to good gliding properties of the tear substitute according to the invention, in addition, because of the resulting fine distribution, it also is responsible for an increased residence duration on the surface. The latter effect is further supported by the fact that the thin film spontaneously seeks the lowest possible layer thicknesses, while the chosen surface and boundary properties at the same time act against rupturing of the films. By an appropriate selection of the components of the tear substitute, the surface tension of the tear substitute and the interfacial tension between the tear substitute and eye surface can be adjusted in such a manner that the sum of the two magnitudes is greater than the surface tension of the surface of the eye. This allows, in particular, improved film formation as a result of spreading on the eye surface. The film-like layer structures produced by spreading can take over the function of the natural tear film, where the cornea is wetted and protected without the need to hydrophilize the cornea surface.

**[0031]** The sliding properties and the residence duration can be further improved if the tear substitute according to the invention is first in the form of a polyaphron gel. It was found that such gels made of the components according to the invention decompose to the liquid condition as a result of the high shear stresses generated during blinking of the eyelid. This decomposition is irreversible as soon as the polyaphron structure is completely destroyed in the entire volume of the gel. It was shown that, as a result of shearing stresses, produced, for example, during the blinking of an eyelid, a certain volume of the gel is released as a result of irreversible liquefaction, and the liquefied portion of the gel is then evenly distributed on smooth surfaces due to spreading of the immiscible components, in the form of a thin film. Advantageously, the gel-form tear substitute is introduced into the conjunctival sac, where it forms a gel-form reservoir. During each blinking of the eyelid, a portion of the gel is liquefied and then it is finely and evenly distributed, in the form of a thin film, over the cornea surface.

**[0032]** With the described preparations according to the invention, the requirements for a tear substitute are successfully and excellently met. In this context, it should be mentioned, in particular, that although individual components intrinsically contribute important functions, it is only the combination of the individual components which allows the combination of the excellent properties of the fluorinated surfactants and the nonpolar components.

**[0033]** In this context, it is particularly the combination of the oxygen-transporting properties and the uptake capacity for water-soluble nutrients with the properties of high transparence and good film formation, which is of crucial importance. In addition to the replacement of functions such as wetting, reduction of abrasion, supply of nutrients and oxygen, additional properties of the preparations can also be used, such as the lipophobic properties of the preparations, leading to a reduction in the deposition of sebum, and the absence of sticking of the eyelid. An additional advantage results from the preservative properties of the nonpolar components of which not all the manufacturing steps must be carried out under sterile conditions. This means the preparations can be sterilized after the manufacture, for example, by treatment at 121°C for 15 min in autoclaves, where the use of additional preservatives can be omitted.

**[0034]** The following examples should further explain the manufacture and the use of preparations according to the invention.

**[0035]** Example 1

0.1 g Fluowet® (trade name, the company Clariant) OTL, 0.9 g water and 99 g perfluorophenanthrene (having a surface tension of  $\sigma = 19 \text{ mNm}$ ) are homogenized, sterilized at 121°C for 15 min, and then applied by means of syringe to a mirror and distributed, where the surface is wetted by an even, nonrupturing film.

**[0036]** Example 2

Polyaphron gels are prepared by known methods from tetraethylpiperazinium salt of perfluorooctanoic acid ( $\sigma = 15.9 \text{ mNm}$ ; 0.1 g), balanced salt solution (BSS); 0.9 g and perfluorophenanthrene ( $\sigma = 19 \text{ mNm}$ ; 99 g) or perfluoroalkylethanol oxethylate ( $\sigma = 19 \text{ mNm}$ ; 0.1 g) BSS (0.9 g) and perfluorophenanthrene ( $\sigma = 19 \text{ mNm}$ ; 99 g), and sterilized at 121°C for 15 min in the autoclave. The gel-form preparations were filled into syringes and investigated by a Draize test. No irritations occurred during the Draize test. Even two weeks after application of the gel, the tear secretion, mucus production or secretion of the lid margin glands in rabbits was not impaired. Even after continuation of daily treatment for 16 weeks, no signs of incompatibility were observed.

**[0037]** Example 3

A preparation prepared according to Example 1 is applied to the eyes of rabbits. A short time after application, a known treatment agent for enlarging the pupils is applied. It was observed that the pupil-enlarging agent loses its effect as soon as a

[illegible]

**[0038]** Example 4

From a 10% solution of perfluorooctanoic acid tetraethylpiperazinium salt (having surface tension  $\sigma = 15.9$  mNm) in water and highly purified silicone oil 1000 mPas, a gel is produced by foaming the aqueous solution and introduction of the silicone oil. After sterilization at 121°C for 15 min, this preparation is applied to a water-loaded surface. Spontaneous spreading occurs.

## TRANSLATION OF THE APPLICATION AS ORIGINALLY FILED

TEAR SUBSTITUTE

The invention relates to a tear substitute for the external treatment of the eye.

Tear substitutes are used in the treatment of diseases of the eye, such as common keratoconjunctivitis sicca (so-called "dry eye"). Dry eye can be the result of different causes. The most frequent causes include reduction in tear production in the elderly, rheumatic or internal diseases (such as polyarthritis, diabetes and thyroid disease), diseases in which antibodies are raised against the body's own physiological substances (Sjögren's disease, Lupus erythematosus, scleroderma), skin diseases, hormonal changes, neuroparalysis (such as after a stroke, defective position of the eyelid, decortication of tear glands), ingestion of certain drugs (such as  $\beta$  blockers, birth control pill, soporifics and tranquilizers), nutritional deficiency, climatic influences (heat, dry environmental air, season, air conditioners), environmental pollution (ozone, dust, solvent vapors, etc.), working in front of monitors, and chronic use of vessel contracting eyedrops (so-called whiteners). Furthermore, such eye diseases are also caused, but less frequently, by autoimmune diseases, diseases of the hematopoietic system, local eye diseases such as inflammation and trauma of the tear glands or hereditary diseases. The resulting dysfunctions impair or prevent the formation of a normal tear film, which has an exceedingly complicated structure in its natural form. There are essentially three components which participate in the formation of the tear film:

An internal mucin layer which covers the epithelial surface, followed by a middle aqueous layer, and a thin, external lipid layer. The mucin layer here functions as an adhesive component for the wetting of the cornea. The aqueous component moisturizes the cornea and it has a cleaning and protective function. The lipid component prevents evaporation of the aqueous component and prevents a quick runoff of the tear film.

Only an intact tear film can guarantee the full functionality of the eye surface over time, and, in addition to the mentioned defects, properties which reduce abrasion, antibacterial properties, and the oxygen supply of the cornea can be of importance. The above-mentioned components of tears are continuously produced. The formation of a thin tear film over the cornea occurs spontaneously with each blink of the eyelid, as, during the downward movement of the upper lid, the external lipid layer of the tear film is compressed between the lid margins, where the aqueous layer essentially remains in its position. As soon as a part of the production of the tear components is interrupted or

disturbed, or there is a mechanical obstacle to the formation of the tear film as a result of the blinking of the eyelid, corresponding complaints arise from, for instance the so-called sand grain effect to massive visual disorders, which in extreme cases, can lead to blindness as a result of irreversible damage to the cornea.

As there are a multitude of possible causes of "dry eye" and as the problem of the tear film [formation] is complex, a multitude of treatment agents are known from the state of the art. In this context, examples are the patents EP 698 388, DE 195 11 322, DE 43 03 818, EP 801 948, WO 97/45102, and WO 96/33695.

In the above-mentioned patents, descriptions are essentially provided of treatment agents which, as a result of introduction into the conjunctival sac, replace one or more missing components of natural tear film. The replacement is here carried out using substances which, having an appropriate retention time, take over the protective and abrasion-reducing functions, and possess the same or at least similar properties as the components to be substituted. The treatment agent which is commercially available under the trade name "Liposic," for example, constitutes an attempt to duplicate all the natural tear components in a so-called three-dimensional tear.

The liquid treatment agents which are known from the state of the art, however, all present the drawback of having a relatively short residence time on the cornea. As a result, the treatment agent must be introduced at regular intervals into the eye, which can be very inconvenient and unpleasant for the patient. In the known gel form treatment agents, this drawback is at least partially avoided. However, in the case of gel form treatment agents, it was shown to be difficult to supply sufficient oxygen to the cornea.

In the patents EP 089 815 and EP 112 658, ophthalmological treatment agents for lubrication and protection of the eye surface are proposed which contain a perfluorocarbon or a substituted derivative thereof. The substantial advantages compared to conventional treatment agents that are mentioned are here the immiscibility with water and the high gas dissolution capacity, particularly for oxygen.

Because of the known high oxygen dissolution capacity of fluorocarbons, the treatment agent described in the above patents is said to guarantee a sufficient oxygen supply for the cornea. In addition, because of the high density of the perfluorocarbons, a long residence time on the cornea is said to be possible because the compounds are said to become enriched due to their high specific weight. Moreover, it is claimed that, because of the insolubility of the treatment agent in water, the use of preservatives could be omitted.





hydrophilic, hydrophobic and fluorophilic properties, resulting from the structure of the fluorinated surfactants, which is used for the wetting of the cornea surface. By maintaining certain concentrations of the fluorinated surfactants it is possible, in addition, to adjust the surface and interfacial tensions of the components of the invention in such a manner that an optimal film formation and sufficient supply of oxygen to the cornea are possible.

The formation of thin films on the cornea surface leads to high residence capacities for the preparations and at the same time to the absence of prevention of tear secretion, mucus production and secretion of the marginal eyelid glands. Additionally, the resulting films prevent adhesion of the lid. In addition, the special surface properties of the preparation allow their passage, at the end of the residence time, into the natural tear drainage ducts without obstructing them. In this manner, the preparations according to the invention can take over the abrasion reducing and wetting functions of natural tear film without causing undesired side effects such as obstructed tear drainage ducts.

As a result of the combination of the components of the tear substitute according to the invention, it is possible to benefit from the advantages of the individual components without having to take into account any drawbacks.

The wetting properties of surfactants are well known, and they are used in many industrial processes. However, it is precisely these intrinsically advantageous properties which are the cause of their poor biocompatibility, which is reflected above all in dysfunctions in cell membranes. Therefore, the use of surfactant-containing substances in medical applications is strongly limited because of toxic behavior. Thus, for example, incompatibilities of oxygen-transporting emulsions can be explained by the effect of the surfactants which they contain. In particular, it appears that the use of surfactant-containing substances as tear substitutes is ruled out, because the function of the natural tear film is decisively effected by the surface-modifying properties of the lipids, and the latter react particularly sensitively to additives of other surfactant substances.

However, by the combination of the components of the tear substitute according to the invention, the surface active effect of the surfactants was, nevertheless, unexpectedly exploited, without impairment of the function of the surfactant compounds present in the natural tear film. The fluorinated surfactants used according to the invention, in this context, are characterized, in contrast to other known surfactants, by an improved biocompatibility. Fluorinated surfactants by themselves offer an improved

biocompatibility, compared to nonfluorine-containing emulsifiers, combined with an unusual surface activity.

In addition, the damaging effects of the fluorinated surfactants in the preparations according to the invention are further repressed by the effects of the nonpolar components. This is achieved by the fixing of the fluorinated surfactants in the nonpolar matrix, resulting in a lowering of the surface tension of the aqueous components, without destroying the conditions which are caused by the natural surfactant compounds of the tear film. In this context, one exploits the fact that the interactions of the fluorinated surfactants with the nonpolar components are stronger than with the lipophilic components of the eye surface.

In this manner, the known surfactant properties of surfactants can be exploited for extraocular applications. In combination with the properties of water and the nonpolar matrix, the fluorinated surfactants provide the film-forming properties of the preparations according to the invention, and thus they allow an even thin-film wetting of the cornea.

As nonpolar components, fluorocarbons or silicone oil are particularly suited. If fluorocarbons are used as nonpolar components, the known advantageous properties of these substances, such as the high oxygen solubility and the lubricating and protecting function, can be exploited. As a result of the oxygen-transporting properties of the fluorocarbons, the cornea is sufficiently supplied with oxygen without impairing vision due to irregular layer thicknesses or milky emulsions, and without the formation of barrier layers between the hydrophobic cornea and the lipophobic fluorocarbons, which prevent oxygen transfer. In this context, it should be emphasized that fluorocarbon does not need a carrier (as, for example, in EP 089 815), rather it acts itself as a carrier for the fluorinated surfactants.

The formation of thin films as a result of the blinking of the eyelid and the spreading of the nonmiscible components not only leads to good gliding properties of the tear substitute according to the invention, in addition, because of the resulting fine distribution, it also is responsible for an increased residence duration on the surface. The latter effect is further supported by the fact that the thin film spontaneously seeks the lowest possible layer thicknesses, while the chosen surface and boundary properties at the same time act against rupturing of the films. By an appropriate selection of the components of the tear substitute, the surface tension of the tear substitute and the interfacial tension between the tear substitute and eye surface can be adjusted in such a manner that the sum of the two magnitudes is greater than the surface tension of the surface of the eye. This allows, in particular, improved film

formation as a result of spreading on the eye surface. The film-like layer structures produced by spreading can take over the function of the natural tear film, where the cornea is wetted and protected without the need to hydrophilize the cornea surface.

The sliding properties and the residence duration can be further improved if the tear substitute according to the invention is first in the form of a polyaphron gel. It was found that such gels made of the components according to the invention decompose to the liquid condition as a result of the high shear stresses generated during blinking of the eyelid. This decomposition is irreversible as soon as the polyaphron structure is completely destroyed in the entire volume of the gel. It was shown that, as a result of shearing stresses, produced, for example, during the blinking of an eyelid, a certain volume of the gel is released as a result of irreversible liquefaction, and the liquefied portion of the gel is then evenly distributed on smooth surfaces due to spreading of the immiscible components, in the form of a thin film. Advantageously, the gel-form tear substitute is introduced into the conjunctival sac, where it forms a gel-form reservoir. During each blinking of the eyelid, a portion of the gel is liquefied and then it is finely and evenly distributed, in the form of a thin film, over the cornea surface.

With the described preparations according to the invention, the requirements for a tear substitute are successfully and excellently met. In this context, it should be mentioned, in particular, that although individual components intrinsically contribute important functions, it is only the combination of the individual components which allows the combination of the excellent properties of the fluorinated surfactants and the nonpolar components.

In this context, it is particularly the combination of the oxygen-transporting properties and the uptake capacity for water-soluble nutrients with the properties of high transparence and good film formation, which is of crucial importance. In addition to the replacement of functions such as wetting, reduction of abrasion, supply of nutrients and oxygen, additional properties of the preparations can also be used, such as the lipophobic properties of the preparations, leading to a reduction in the deposition of sebum, and the absence of sticking of the eyelid. An additional advantage results from the preservative properties of the nonpolar components of which not all the manufacturing steps must be carried out under sterile conditions. This means the preparations can be sterilized after the manufacture, for example, by treatment at 121°C for 15 min in autoclaves, where the use of additional preservatives can be omitted.

The following examples should further explain the manufacture and the use of preparations according to the invention.

#### Example 1

0.1 g Fluowet® (trade name, the company Clariant) OTL, 0.9 g water and 99 g perfluorophenanthrene (having a surface tension of  $\sigma = 19$  mNm) are homogenized, sterilized at 121°C for 15 min, and then applied by means of syringe to a mirror and distributed, where the surface is wetted by an even, nonrupturing film.

#### Example 2

Polyaphron gels are prepared by known methods from tetraethylpiperazinium salt of perfluorooctanoic acid ( $\sigma = 15.9$  mNm; 0.1 g), balanced salt solution (BSS); 0.9 g and perfluorophenanthrene ( $\sigma = 19$  mNm; 99 g) or perfluoroalkylethanol oxethylate ( $\sigma = 19$  mNm; 0.1 g) BSS (0.9 g) and perfluorophenanthrene ( $\sigma = 19$  mNm; 99 g), and sterilized at 121°C for 15 min in the autoclave. The gel-form preparations were filled into syringes and investigated by a Draize test. No irritations occurred during the Draize test. Even two weeks after application of the gel, the tear secretion, mucus production or secretion of the lid margin glands in rabbits was not impaired. Even after continuation of daily treatment for 16 weeks, no signs of incompatibility were observed.

#### Example 3

A preparation prepared according to Example 1 is applied to the eyes of rabbits. A short time after application, a known treatment agent for enlarging the pupils is applied. It was observed that the pupil-enlarging agent loses its effect as soon as a thin film of the tear substitute according to the invention has formed on the cornea. This observation serves as a demonstration of the capacity of the preparation according to the invention to form thin closed films over the cornea, as with the natural tear. In addition, this example shows that the preparations according to the invention have a protective function, by preventing water-containing or water-soluble substance from coming in contact with the eye surface as soon as a film has formed on the cornea.

#### Example 4

From a 10% solution of perfluorooctanoic acid tetraethylpiperazinium salt (having surface tension  $\sigma = 15.9$  mNm) in water and highly purified silicone oil 1000 mPas, a gel is produced by foaming the aqueous solution and introduction of the silicone oil. After sterilization at 121°C for 15 min, this preparation is applied to a water-loaded surface. Spontaneous spreading occurs.

## TRANSLATION OF AMENDED CLAIMS

Claims

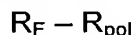
1. Use of a gel, which contains at least one water-soluble fluorinated surfactant, water and a nonpolar component, which is a fluorocarbon, for the manufacture of a tear substitute.

2. Use of a gel, which contains at least one water-soluble fluorinated surfactant, water and a nonpolar component, which is silicone oil, for the manufacture of a tear substitute.

3. Use according to Claim 1 or Claim 2, characterized in that the fluorocarbon is chosen from the group which comprises perfluoro compounds, partially fluorinated compounds having the general formula  $R_F R_H$  or  $R_F R_H R_F$ , as well as fluoro oligomers of the type  $(R_F)_x R_H$ , or a mixture thereof.

4. Use according to one of the preceding claims, characterized in that it is in the form of a gel and presents a polyaphron structure.

5. Use according to one of the preceding claims, characterized in that the fluorinated surfactant is prepared according to the formula:



where  $R_F$  represents a linear or branched perfluoroalkyl group having more than 5 carbon atoms and  $R_{pol}$  represents a polar hydrocarbon residue which comprises at least one functional group, chosen from the series:

CO-NH(R), CO-NH(R)<sub>2</sub>, COO<sup>-</sup>, COOR, SO<sub>3</sub><sup>-</sup>, SO<sub>2</sub>-N(R)<sub>2</sub>, CH<sub>2</sub>-O-, R, PO<sub>2</sub>H, PO<sub>3</sub>H<sub>2</sub>,

where R represents an alkyl.

6. Use according to one of the preceding claims, characterized in that the molecular weight of the fluorinated surfactants is greater than 400 g/mol, and the surface tension of the fluorinated surfactants in an aqueous solution is smaller than 30 mNm.

7. Use according to one of the preceding claims, characterized in that the concentration of the fluorinated surfactant is less than the critical micellar formation concentration, preferably less than 0.1%, and the concentration of the fluorocarbon is greater than 60 wt%, preferably greater than 90 wt%.

8. Use according to one of the preceding claims, characterized in that the water-soluble fluorinated surfactant presents at least six completely fluorinated hydrocarbons.

9. Use according to one of the preceding claims, characterized in that it presents a refractive index of 1.334-1.338.

10. Use according to one of the preceding claims, characterized in that the tear substitute forms a thin film on the cornea.

11. Use according to one of the preceding claims, characterized in that the sum of the surface tension of the tear substitute and the interfacial tension between the tear substitute and the eye surface is smaller than the surface tension of the eye surface.

12. Use according to one of Claims 4-11, characterized in that the gel becomes at least in part irreversibly liquefied under the effect of shearing stresses.

13. Use according to Claim 12, characterized in that it can be introduced into the conjunctival sac, where the tear substitute forms a gel-form reservoir, part of which liquefies during each movement of the eyelid.

14. Use according to Claim 13, characterized in that the liquefied part of the tear substitute on the cornea forms a thin film.

15. Method for the manufacture of a tear substitute, which contains at least one water-soluble fluorinated surfactant, water and a nonpolar component, which is a fluorocarbon.

16. Method for the manufacture of a tear substitute, which contains at least one water-soluble fluorinated surfactant, water and a nonpolar component which is a silicone oil.

17. Method according to one of Claims 15 or 16, characterized in that the composition of the water-soluble fluorinated surfactant, water and the nonpolar component is sterilized after its preparation.

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**DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled

**ARTIFICIAL TEAR REPLACEMENT SOLUTION**

the specification of which: (check one)

\_\_\_\_\_ is attached hereto.

  X   was filed on INTERNATIONAL DATE – JUNE 30, 2000  
under Attorney's Docket Number  
as Application Serial No. PCT/EP00/06109  
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information material to the patentability of this application in accordance with 37 CFR 1.56.

I hereby claim the benefit of foreign priority under 35 USC 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application the priority of which is claimed:

Prior Foreign Application(s):			Priority Claimed	
Number	Country	Filing Date	Yes	No
199 38 668.4	GERMANY	AUG. 14, 1999	X	

I hereby claim the benefit under 35 USC 119(e) of any United States provisional application(s) listed below

Application Number	Filing Date

I hereby claim the benefit of United States priority under 35 USC 120 of any United States application(s) or 365(c) of any PCT international applications designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is disclosed in a listed one of the prior United States or PCT international application in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose information material to the patentability of this application as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Parent Application or PCT Parent Number	(Filing Date)	Parent Patent Number
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POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

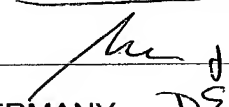
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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